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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/799,922	03/12/2004	Hans Ernst Jan Hofland	020681-001610	6834

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1612	

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05/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,922	HOFLAND ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 6-42* is/are pending in the application.

4a) Of the above claim(s) *6-38,40 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,39 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 2-21-09 is acknowledged.

Claims included in the prosecution are 1, 39 and 42. Applicant indicates the withdrawal of claims 6, 11, 38 and 41. It should be noted that these were not subjected to restriction and applicant has voluntarily

In view of the amendments, the previous 112 first paragraph (new matter) and the second paragraph rejection and the 102 rejections are withdrawn.

Claim Rejections - 35 USC § 112

1. Claims 1, 39 and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro inhibition of HSV and HIV by octylglycerol containing liposomes, does not reasonably provide enablement for generic 'a fatty acid monoglyceride of the formula in claim 1 and prevention of enveloped viral infection . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d, 1400 (Fed.Cir.1988). Among these factors are: (1) the nature of the invention; 2) the state of the prior art; 3) the relative skill of those in the art; 4) the predictability or unpredictability of the art; 5) the breadth of the claims; 6)

the amount of direction or guidance presented; 7) the presence or absence of working examples; and 8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

1) The nature of the invention: the invention concerns with a method of prevention of an infection using a liposomal formulation containing a fatty acid monoglyceride of the formula in claim 1.

2) The state of the prior art: the state of the prior art is very high in terms of formulating the liposomal compositions containing specific drugs for the treatment of various diseases but not preventing disease with a generic term, infection which can be due to any microorganism.

3) The relative skill of those in the art: the skill of one of ordinary skill in the art is very high (Ph.D level technology).

4) The predictability or unpredictability in the art: while there is general predictability in formulating the liposomal or proliposomal formulations, there is unpredictability in the art of preventing disease states such as AIDS, HSV infections and other viral diseases. Infections can be caused by any organism including, viruses, bacteria, micobacteria, fungi and parasites. Just because one specific compound (octyl glycerol) inhibits a specific virus in vitro, one cannot extrapolate the results to prevention of the infection by that specific virus in vivo by any other single chain lipid, let alone prevent any infection caused by any other infectious agent. Recent well-known example of drug resistant strain of tuberculosis can be cited as interest. Furthermore, in vitro studies may or may

not be enough to predict a compound's effect in vivo and the examiner cites the reference of Zips (In Vivo, 19, pp. 1-8, 2005) in this context (see page 1 (Translational research chain in evaluation of anticancer agents on col. 2, page 1 and page 3, col. 2, last but one para).

5) The breadth of the claims: instant claim is very broad in terms of the active agent and the viral diseases to be prevented. Said claim 1 does not recite any specific active agent and the specific viral disease to be prevented. There are several enveloped viruses and it is well known in the art that there are no specific drugs which can be effectively used against these viruses let alone prevent the diseases caused by these viruses.

6) The amount of direction of guidance provided: instant specification provides no guidance at all in terms of preventing disease states.

7) The presence or absence of working examples: as pointed out above, infection can be caused by any microorganism and instant specification provides no working examples as to how the diseases can be prevented using the claimed formulation. What is shown in the examples is the use of one specific compound, 'octylglycerol' on specific viruses HSV and HIV in vitro.

8) The quantity of experimentation necessary: since the claim 1 does not recite any specific active agent and prevention of any specific disease state, it is difficult for one of ordinary skill in the art to choose the proper active agent and prevent a disease without undue experimentation.

These arguments are not persuasive. As already pointed out what is shown in the specification is the ***in vitro*** effectiveness of octylglycerol against the claimed

viruses. Based on these studies applicant drafts the claims drawn to prevention of viral infection caused by HSV or HIV. First of all, just because they are effective in vitro in killing these viruses, one cannot extrapolate the results to ***prevention*** of these viral infections. When one cannot predict the effectiveness of the composition in treating, it is unclear to the examiner how one can predict the prevention of the HIV and HSV infections from occurring at all. The examiner has already advised applicant to note Ex parte Balzarini 21 USPQ2d, 1892 at page 1897 (Bd. PAT. App. and Int. 1991): We do not presume to tell appellants what evidence would be acceptable in rebuttal of these rejections. While we are not requiring human clinical trials, it may well be that in 1987 or even now those skilled in this art would not accept anything short of such human clinical trials. There is no evidence of record that experimental animal models have been developed in this area which would have been predictive of human efficacy. The examiner also cites references which show the ineffectiveness of the microbicidal, nonoxynol-9 in prevention of HIV infections, though this compound was shown to be an effective barrier to HIV in laboratory studies (Public Health Agency of Canada, April 2003; The Bay Area Reporter, November, 2000) and the ineffectiveness of Carraguard, one of the highly developed candidates in this field which failed to prevent HIV transmission in a Phase III trial (Bioactive Polymers, 6-9-08). Furthermore, according to the specification the compositions can be topical formulations, oral formulations, nasal formulations, ophthalmic formulations and even parenteral formulations. Instant specification does not teach adequately how the prevention of HIV and HSV infections

can be accomplished by just by application to the eye or other modes of administration claimed.

The rejection is maintained.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1, 39 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eibl (US 2002/0173489) in combination with Ho (US 2004/0208921, Hostetler (US 2001/0033862), Firshein (6,121,245) individually or in combination.

Eibl discloses formulations containing single chain lipids, which include alkylglycerols for viral infections such as HIV (0028, 0049-0057, 0064-0066, 0089,

claims, claims 21, 26, 49, 51, 52, 54 and 57). What is lacking in Eibl is the teaching of the use of liposomes as carriers for the alkylglycerols.

Ho while disclosing liposomal formulations containing drugs for targeted delivery to lymphoid tissues teaches the advantages of liposomes or lipid complexes. According to Ho, as drug delivery systems, liposomes are especially promising because they can modulate the pharmacokinetics of liposome-associated drugs, which is not possible with non-lipid associated, or free drugs. Any number or combinations of lipid-anti HIV drug or lipid-anti-HIV biological complexes can be subcutaneously injected into HIV infected mammalian subject so that high concentrations of stable lipid-drug complexes can be preferentially delivered to the lymphoid tissue via lymphatic vessels, instead of delivering intravenously and HIV reservoirs within the infected lymphoid cells can be targeted effectively (abstract, 0004, 0009, 0013-0015, 0028, 0031, 0033, 0035, examples and claims). One of the lipids, which could be used, in addition in the liposomes is monoglycerides (alkylglycerols) (0034).

Hostetler while disclosing a method of treating viral infections teaches that in the form of liposomes, the antiviral agents are preferentially taken up by macrophages and monocytes, cells which have been found to harbor the target HIV virus (abstract, 0014, 0050 and 0051).

Firshein teaches while disclosing a method of treating cancer using alkylglycerols teaches that these compounds that these compounds can be incorporated into liposomes and that ordinary glycerol ethers, after incorporation into phospholipids, can activated the body's immune defense system (col. 4, lines 55-61; col. 10, lines 4-20).

It would have been obvious to one of ordinary skill in the art to use liposomes as carriers for alkylglycerols taught by Eibl because of the advantages of liposomes taught by Ho, Hostetler and Firshein.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that the claims are directed to methods of using liposomal formulations (sic) octylglycerols for the prevention of the viral infections and that Eibl teaches "medicament which contains as active material at least one compound of the formula R-Y-P_2-X-R_1 and it does not suggest in Eibl's reference that the active agent is alkylglycerol and alkylglycerol is used merely in combination with the above described active compound. This argument is not persuasive since in 0050 Eibl teaches synergistic compositions containing octylglycerol which means alkylglycerols by themselves have some activity and instant claim language does not exclude other compounds taught by Eibl. Applicant argues that Eibl does not teach liposomes. This argument is not persuasive since Eibl is combined with references which teach liposomes. Applicant argues that in the office action dated Feb. 21, 2008, the examiner notes that methods taught by Eibl are drawn to preventing proliferation and not preventing infection and since viruses such as HIV remain dormant and the antiviral agents actually prevent proliferation of the virus. This argument is not persuasive. First of all, instant claims do not recite the limitation of prevention of the viruses from coming out of the dormant state or even the prevention of viruses from entering the host. Secondly, Eibl teaches treating a patient with a viral infection which includes even infection by the virus, but in a dormant state.

Claims 1, 39 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isaacs (5,466,714) or Thormar (6,596,763) in combination with Ho (US 2004/0208921, Hostetler (US 2001/0033862), Firshein (6,121,245) individually or in combination.

Isaacs discloses prophylaxis of enveloped viruses such as HIV using fatty acid monoglycerides which include octylglycerol as ***active agents*** (abstract, col. 8, line 41 through col. 11, line 15; col. 13, line 35 through col. 15, line 15; col. 19, line 30 through col. 20, line 65; col. 22, lines 30-36 and claim 1).

Thormar discloses fatty acid monoglycerides which include octylglycerol as ***active agents*** for the prevention and treatment of enveloped viruses. The viruses include HIV and HSV and administration includes topical mode (col. 3, line 30 through col. 4, lines 52; col. 5, line 31 through col. 9, line 67; Examples and claims).

These references do not teach liposomes as carriers.

Ho while disclosing liposomal formulations containing drugs for targeted delivery to lymphoid tissues teaches the advantages of liposomes or lipid complexes. According to Ho, as drug delivery systems, liposomes are especially promising because they can modulate the pharmacokinetics of liposome-associated drugs, which is not possible with non-lipid associated, or free drugs. Any number or combinations of lipid-anti HIV drug or lipid-anti-HIV biological complexes can be subcutaneously injected into HIV infected mammalian subject so that high concentrations of stable lipid-drug complexes can be preferentially delivered to the lymphoid tissue via lymphatic vessels, instead of delivering intravenously and HIV reservoirs within the infected lymphoid cells can be targeted effectively (abstract, 0004, 0009, 0013-0015, 0028, 0031, 0033, 0035,

examples and claims). One of the lipids, which could be used, in addition in the liposomes is monoglycerides (alkylglycerols) (0034).

Hostetler while disclosing a method of treating viral infections teaches that in the form of liposomes, the antiviral agents are preferentially taken up by macrophages and monocytes, cells which have been found to harbor the target HIV virus (abstract, 0014, 0050 and 0051).

Firshein teaches while disclosing a method of treating cancer using alkylglycerols teaches that these compounds that these compounds can be incorporated into liposomes and that ordinary glycerol ethers, after incorporation into phospholipids, can activated the body's immune defense system (col. 4, lines 55-61; col. 10, lines 4-20).

It would have been obvious to one of ordinary skill in the art to use liposomes as carriers for alkylglycerols taught by Isaacs or Thormar because of the advantages of liposomes taught by Ho, Hostetler and Firshein.

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore /
Primary Examiner, Art Unit 1612

GSK